

## REMARKS

### The Amendments

In order to advance prosecution, Applicants have added a new independent claim 37 and dependent claims 38-40, and have canceled claims 1, 2, 4-15, 18-20, 22, 25, 26, 28, 29, 31, 32, and 34-36. Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

### Priority

The Office Action alleged that the instant application was not entitled to priority of International Patent Application PCT/US03/05028 and U.S. Provisional Applications 60/358,580, 60/363,124, 60/386,782, 60/393,796, 60/399,348, 60/406,784, 60/408,378, 60/409,293, and 60/440,129. The applicants respectfully disagree.

The present application claims priority to, *inter alia*, 60/363,124 (the '124 application), filed March 11, 2002. The claims presented above all find support in, *inter alia*, the '124 application. In particular, new independent claim 37 finds support for chemically synthesized double stranded siRNA at p. 3, lines 15-17; p. 32, lines 11-12; p. 35, lines 29-30, and p. 60, line 20; complementarity between the first and second strands at p. 3, lines 7-9, p. 12, lines 4-7, p. 19, lines 11-14, p. 21, lines 3-6, and p. 25, lines 17-29; one strand having between 18-24 nucleotides complementary to SNCA RNA at p. 18, lines 1-5, p. 60, lines 18-21, p. 297, entry in Table III for GenBank Accession No. NM\_000345; and at least one sugar modification at p. 6, line 19 to page 8, line 10, and p.36, lines 1, 13, and 19-31.

Support for the dependent claims can also be found in, *inter alia*, the '124 application:

Claim	Support
3	siRNA comprising one or more ribonucleotides: p. 14, lines 3-9.
16	Terminal cap at 5', 3', or both 5' and 3' ends of first strand: p. 10, lines 6-7, 20-21, p. 11, lines 1-2, 15-16, p. 40, lines 1-18.

Claim	Support
17	Inverted abasic moiety: p. 40, line 10, p. 13, line 18 to p. 14, line 13.
21	One or more phosphorothioate internucleotide linkages: p. 5, line 15, p. 5, line 23 to p. 6 line 18, p. 9 line 14 to p. 10, line 2, p. 11, lines 26-28.
23	Each of the two strands of said siNA molecule comprise 21 nucleotides: p. 12, lines 4-12, p. 26, lines 3-5.
24	21 nucleotides with 19 base pairs and at least two non base-paired nucleotides at 3'-ends: : p. 12, lines 4-12, p. 26, lines 3-5
27	Perfectly complementary: p. 25, lines 27-29.
30	Phosphate group: p. 8, line 26 to p. 9, line 13.
33	Pharmaceutical composition: p. 18, lines 15-19.
38	2'-O-methyl (O-Me): p. 5, line 15, p. 6, line 24 (R3 = O-alkyl), p. 10, lines 5, 9, 13, 19, 23, 27, 33, p. 11 lines 4, 8, 14, 17, 22.
39	2'-deoxy-2'-fluoro (F): p. 5, line 15, p. 6, line 24 (R3 = F), p. 10, lines 5, 9, 13, 19, 23, 27, 33, p. 11 lines 4, 8, 14, 17, 22.
40	2'-deoxy (H): p. 6, line 23 (R3 = H), p. 10, lines 5, 9, 13, 19, 23, 27, 33, p. 11 lines 4, 8, 14, 17, 22.

### **The Sequence Listing**

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO:311. The sequence represents GenBank entry NM\_000345. The version of NM\_000345 appearing in the sequence listing as SEQ ID NO:311 appeared in GenBank on February 6, 2001. The sequence listing adds no new matter and applicants respectfully request its entry.

### **Information Disclosure Statements**

Applicants filed a Supplemental Information Disclosure Statement on June 8, 2005 along with a PTO form 1449. We have not received the PTO form 1449 initialed by the Examiner. A copy of the 1449 is enclosed. Applicants respectfully request that the Office initial and return the 1449.

### **Rejection of Claim 36 Under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 101**

Claim 36 stands rejected under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 101. Claim 36 has been cancelled. The rejection is therefore moot. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 13-15, 18-20, 28, 29, 34, and 35 under 35 U.S.C. § 112 second paragraph**

Claims 13-15, 18-20, 28, 29, 34, and 35 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 13-15, 18-20, 28, 29, 34, and 35 have been cancelled. The rejection is therefore moot. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 1-35 Under 35 U.S.C. § 112, second paragraph**

Claims 1-35 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Claims 1, 2, 4-15, 18-20, 22, 25, 26, 28, 29, 31, 32, and 34-36 have been cancelled. The rejection is therefore moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 3, 16, 17, 21, 23, 24, 27, 30, and 33.

Claims 3, 16, 17, 21, 23, 24, 27, 30, and 33 have been amended so that they are dependant on new claim 37. New claim 37 recites a chemically synthesized double stranded siNA molecule consisting essentially of a first nucleic acid strand and a second nucleic acid strand. The first strand has complementarity to the second strand. The second strand has 18-24 nucleotides complementary to a human synuclein-1 (SNCA) RNA comprising SEQ ID NO:311.

The Office Action recognizes that “claims to siNA sequences directed to human SNCA RNA (Isoform NM\_000345)...meet the written description requirement of 35 USC 112, first paragraph”. See, Office Action paragraph 13. Claim 37 recites siNA molecules having complementarity to human SNCA RNA (Isoform NM-000345, SEQ ID NO:311. The Office Action agrees that siNA sequences directed to human SNCA RNA have adequate written description. Therefore, the claims have adequate written description.

Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 1, 3-11, 23, 27-30, and 33-35 Under 35 U.S.C. § 102(b)**

Claims 1, 3-11, 23, 27-30, and 33-35 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 01/49844. Claims 1, 3-11, 28, 29, 34 and 35 have been canceled. The rejection is therefore moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 3, 23, 27, 30, and 33.

Anticipation under 35 U.S.C. § 102 requires the presence in a single prior art disclosure of each and every element of a claimed invention. *Lewmar Marine Inc. v. Barient Inc.*, 3 USPQ2d 1766, 1767 (Fed. Cir. 1987).

WO 01/49844 does not teach each and every element of the claims. For example, WO 01/49844 does not teach or suggest chemically synthesized double stranded short interfering nucleic acid molecules. Additionally, WO 01/49844 does not teach or suggest a double stranded siNA molecules having at least one sugar modification. Instead, WO 01/49844 teaches inverted repeat (IR) gene construct expression vectors encoding double stranded RNA. WO 01/49844 describes long double stranded RNA and does not describe siNA. There is no teaching or suggestion of chemically synthesized or chemically modified double stranded short interfering nucleic acid molecules targeting SNCA in WO 01/49844. Therefore, WO 01/49844 cannot anticipate the claims.

The Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 1, and 33-35 Under 35 U.S.C. § 102(e)**

Claims 1 and 33-35 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Bumcrot *et al.*, WO 2005/004794. Claims 1, 34 and 35 have been canceled. The rejection is therefore moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claim 33.

WO 2005/004794 has an effective filing date of June 9, 2003, which is after the effective filing date of the instant invention, March 11, 2002. Therefore, WO 2005/004794 is not prior art to the instant application. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claims 13-16 and 18-20 Under 35 U.S.C. § 103(a)**

Claims 13-16 and 18-20 stand rejected as allegedly obvious over WO 01/49844; WO 03/099298; and Ueda *et al.*, (1993). Claims 13-15 and 18-20 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claim 16.

Initially, the instant application has a priority date of at least March 11, 2002. (US 60/363,124). WO 03/099298 claims a priority date of May 24, 2002. Therefore, WO 03/099298 does not constitute prior art to the present claims.

The amended claims recite chemically synthesized double stranded short interfering nucleic acid (siNA) molecule consisting essentially of a first nucleic acid strand and a second nucleic acid strand. The first strand has complementarity to the second strand. The second

strand has 18-24 nucleotides complementary to a human synuclein-1 (SNCA) RNA comprising SEQ ID NO:311. The siNA molecule has at least one sugar modification.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. See, M.P.E.P. §2143.

Initially, the references do not teach all the claim limitations. For instance, neither WO 01/49844 nor Ueda teach or suggest a chemically synthesized double stranded siNA molecule. Additionally, neither reference teaches or suggests a double stranded siNA molecule that has at least one sugar modification or terminal cap modification.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315, 1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir.1985). Neither reference, alone or in combination, suggests the chemically synthesized double stranded siNA molecules of the claims.

WO 01/49844 is directed to expressed inverted repeat dsRNA technology, not chemically synthesized siNA. There is no teaching or suggestion of chemically synthesized or chemically modified double stranded short interfering nucleic acid molecules targeting SNCA. Since vector expressed inverted repeat long dsRNA and chemically synthesized siNA are completely different approaches to silencing gene expression, WO 01/49844 provides no suggestion or motivation to target SNCA by chemically synthesized short interfering nucleic acid molecules as presently claimed or any siNAs, as this technology was not yet known at the time of the filing date of WO 01/49844.

Ueda does not remedy the deficiencies of WO 01/49844. Ueda merely describes the molecular cloning of a cDNA for human AD amyloid. Ueda does not contemplate SNCA variants comprising SEQ ID No: 311. Additionally, Ueda does not teach or suggest RNAi or siNA technologies. There is no suggestion or motivation to combine the teachings of WO 01/49844 with Ueda to produce the instant invention. Additionally, there is no reasonable expectation of success.

The Office has not established a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the rejection.

**Rejection of Claim 12 Under 35 U.S.C. § 103(a)**

Claim 12 stands rejected as allegedly obvious over WO 01/49844; WO 03/099298; and Ueda *et al.*, (1993) as applied above, and further in view of U.S. Patent Application Publication 2004/0058886. Claim 12 has been canceled. Therefore, the rejection is moot and applicants respectfully request its withdrawal.

**Rejection of Claims 17 and 21 Under 35 U.S.C. § 103(a)**

Claims 17 and 21 stand rejected as allegedly obvious over WO 01/49844; WO 03/099298; and Ueda *et al.*, (1993) as applied above, and further in view of Parrish *et al.*, (2000); and U.S. Patent 5,998,203. Applicants respectfully traverse the rejection.

Initially, the instant application has a priority date of at least March 11, 2002. (US 60/363,124). WO 03/099298 claims a priority date of May 24, 2002. Therefore, WO 03/099298 does not constitute prior art to the present claims.

As discussed above, WO 01/49844 and Ueda do not teach or suggest the claimed invention. Parrish does not teach or suggest nucleic acid interference in mammals. Rather, Parrish discusses a *C. elegans* system. Additionally, Parrish teaches away from the instant invention. Significantly, Parrish reports that dsRNA triggers having between 14 and 23 uninterrupted nucleotide identity to the target induced no interference. *See*, page 1079, right col. Finally, Parrish does not teach or suggest targeting SNCA with siNAs.

The '203 patent does not teach or suggest the use of RNAi, siRNA. Rather, the '203 patent teaches ribozyme technology. Additionally, the '203 patent does not teach or suggest the regulation of SNCA. None of the cited art teaches siNA molecules with sugar modifications or terminal cap modifications.

The cited references, in combination, do not teach all elements of the claims and do not teach or suggest the instant claims. Applicants respectfully request withdrawal of the rejection.

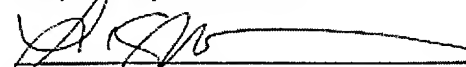
**Rejection of Claims 2, 31, and 32 Under 35 U.S.C. § 103(a)**

Claims 2, 31, and 32 stand rejected as allegedly obvious over WO 01/49844; WO 03/099298; and Ueda *et al.*, (1993) as applied to claims 13-16 and 18-20 above, and further in view of Voinnet *et al.*, (1998). Claims 2, 31 and 32 have been canceled. Therefore, the rejection is moot and applicants respectfully request its withdrawal.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Date: September 20, 2005

Respectfully submitted,



Lisa M.W. Hillman

Registration No. 43,673

Telephone: 312-913-0001  
Facsimile: 312-913-0002

**McDonnell Boehnen Hulbert & Berghoff LLP**  
300 South Wacker Drive  
Chicago, IL 60606